REMARKS

Claim Rejections Under 35 U.S.C. §101 and § 112, first paragraph

Claims 44-46 and 49-52 stand rejected under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility. Claims 44-46 and 49-52 also stand rejected under 35 U.S.C. 112, first paragraph as allegedly not being supported by either a credible, specific and substantial asserted utility or a well established utility.

The Examiner indicates that Applicants arguments submitted in the Reply Brief received 17 January 2006 have been fully considered but are allegedly not found persuasive. Applicants disagree with each of the Examiner's arguments on a number of grounds. The Examiner's arguments will be addressed in order.

(1) The Office Action states that the specification asserts that PRO269 polypeptides are elevated in tumor tissues based on gene amplification results; however, the literature allegedly evidences that this assumption is a false one. Regarding rare tumor markers, such rare tumor markers are only useful if the type of rare tumor it identifies is known. The specification allegedly has not identified anything rare or anything in common among the lung tumor samples in which the PRO269 gene is amplified.

Initially the Examiner made the argument that "only eight out of seventeen lung tumor samples tested positive" and "PRO269 was not amplified in any of the seventeen **colon** tumor samples" (emphasis added) (Examiner's Answer, pages 4-5). In this regard, the Examiner seemed to indicate that a tumor marker is patentable only if the marker tests positive in a statistically high number of samples compared to the total number of samples tested or if the tumor tests positive in every tissue type that was studied. However, this is not legally correct. Neither the M.P.E.P. nor the Utility Guidelines require that it is necessary for the Appellant to show a positive result in most or a larger percentage of the tissue samples studied in order to make an assertion of utility, nor are they needed to show that the tumor marker identifies cancers of various tissues types, *e.g.*: lung, colon, etc.

In response the Applicant argued that it is well-accepted in the art that not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, even if the association of a

tumor marker with a particular type of tumor lesion is rare, or, even if the occurrence of a particular kind of tumor lesion itself is rare, since such markers identifying rare tumors, they have great value in tumor diagnosis, and consequently, in tumor prognosis. The ΔCt values for PRO269 of at least 1-2 ΔCt units, which correspond to $2^{1.04}$ -$2^{1.80}$- fold amplification or 2.056 to 3.482 fold amplification in primary lung tumors, were considered significant according to the Goddard declaration.

The Examiner now argues that the specification has not identified anything rare, or anything in common among the lung tumor samples in which the PRO269 gene is amplified. This is incorrect. The specification indicates that PRO269 is overexpressed in various lung tumors. PRO269 was not overexpressed in the other cancers tested, such as colon cancer. Accordingly, PRO269 has utility as a lung tumor marker. It is not a legal requirement that PRO269 distinguish between different types of lung cancers, ie. squamous cell carcinomas, adenocarcinomas etc. The Examiner is applying an incorrect test.

Applicants maintain that this rejection is improper for these reasons and the reasons previously presented and request withdrawal of this rejection.

(2) The Office action indicates that the Goddard declaration has been considered but is not found to be persuasive. The Office action questions whether or not a 1.04 to 1.8 ΔCt unit amplification in multiple lung tumors is significant, since half of the lung tumor samples did not show an amplification of the gene encoding PRO269. For the reasons set forth above, Applicants maintain that Applicants do not need to show amplification of PRO269 in every lung tumor cell in order for the results to be significant.

First Applicants note that the case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[1] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of

[1] *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

argument"[2] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"[3]. Appellants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[4] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered."

Secondly Applicants have provided two references in which a 2 fold amplification was held to be significant. Applicants note that Orntoft *et al.*, (made of record in Applicant's response filed November 3, 2004 and attached hereto as Exhibit 2) states that chromosomal areas with more than a 2-fold gain in DNA showed a corresponding increase in mRNA transcripts. (abstract) Additional supportive teachings were also provided by Pollack *et al.*, (also of record in response filed November 3, 2004) who studied a series of primary human breast tumors and showed that "62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." (emphasis added) Applicants note that they have shown a more than 2-fold amplification of PRO269 DNA in Example 92.

Accordingly, Applicants request withdrawal of this rejection.

(3) In support of the assertion that there is a poor correlation between mRNA levels and protein levels, the Examiner cites Greenbaum, Pennica *et al.*, Konopka *et al.* Chen et al., LaBaer, Hu et al., Haynes et al., Gygi et al., Lian et al., and Fessler et al.

Applicants disagree for the reasons set forth in their Reply Brief (now designated as a Response to Non-final Office Action) and in their Supplemental Response. The test is whether it is more likely than not that overexpression of the mRNA results in overexpression of the

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[2] *In re Alton,* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[3] *In re Alton, supra.*

[4] Part IIB, 66 Fed. Reg. 1098 (2001).

protein. In order to meet that standard, the Examiner must provide evidence that it is more likely than not that gene amplification does not result in overexpression. Accordingly, Applicants maintain that the Examiner has not met the burden.

On the other hand, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. The articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed November 3, 2004) collectively teach that in general, gene amplification increases mRNA expression. Accordingly, this rejection is improper.

The Examiner cites Pennica *et al.*, Konopka *et al.* in support of the Office position. References Pennica and Konopka were discussed previously in the Reply Brief and Applicants maintain, for the reasons set forth therein, that they cannot be used to establish a poor correlation between mRNA and protein because these references did not show that, in general, it is more likely than not for mRNA and protein levels not to have a correlation. The reasons were clearly discussed in the Reply Brief. Accordingly, the Examiner has not met her burden of proof.

The Examiner cited Pennica *et al.* as providing general evidence showing lack of correlation between gene (DNA) amplification and elevated mRNA levels. (Examiner's Answer, pages 5, 10, 14 and 18). The standard, however, is not absolute certainty. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . ." (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Accordingly, Applicants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes in human colon tumors. Pennica *et al* has no teaching about lung tumors. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

The Examiner cited Konopka *et al.* to establish that protein expression is generally not related to gene amplification. Appellants submit that the PTO has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph^1 template." (See Konopka *et al.*, Abstract, emphasis added).

The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. It is not enough to show that for a particular gene a correlation does not exist. The law requires that the Examiner show evidence that it is more likely than not that such correlation, in general, does not exist. Such a showing has not been made.

The Examiner offers Hu *et al.* as allegedly analyzing 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray. The Examiner states that based on Hu *et al.* the skilled artisan allegedly would not reasonably expect PRO269 protein can be used as a cancer diagnostic.

In their Reply Brief, Applicants discussed the reasons why Hu *et al.* did not establish a *prima facie* case for lack of utility. Applicants rely on the arguments presented therein. The Hu *et al.* reference drew conclusions based upon statistical analysis of information obtained from published literature, and not from experimental data. The statistical analysis by Hu *et al.,* is not a reliable standard because the frequency of citation only reflect the current research interest of a molecule but not the true biological function of the molecule. Accordingly, Hu *et al.* is not sufficient evidence to show that it is likely that PRO269 protein is not overexpressed. The Examiner does not present any meaningful arguments why these criticisms wrong. Accordingly, Hu et al. is irrelevant to the instant discussion.

The Examiner states that Dr. LaBaer allegedly made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between the samples. Similarly, the comments by LaBaer *et al.* is also based on statistical analysis like Hu, and offers an automated literature mining tool termed MedGene to comprehensively summarize gene-disease relationships. As was argued in the Hu reference, "some molecules may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes." Statistical analysis using literature mining is a very useful tool to assist the researcher in their analysis but may greatly over represent or under represent certain genes and thus their conclusions may not be generally applicable. Accordingly, the statements by LaBaer are misplaced here.

The Examiner cites Chen et al. as allegedly comparing mRNA and protein expression for a cohort of genes in the same lung carcinomas. "Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels". Chen et al., allegedly clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products' (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp.311-312). The manner in which the Chen data was averaged and analyzed is a vastly different manner from that of the instant specification. For example, Chen *et al.* studied expression levels across a set of samples which included a large number of tumor samples (76) and a much smaller group of normal samples (9). The authors determined the global relationship between mRNA and corresponding protein expression using the average expression values for all 85 lung tissue samples. A review of the correlation coefficient data presented in the Chen *et al.* paper indicates that, in fact, Chen teaches that 'it is more likely than not' that increased mRNA expression correlates well with increased protein expression. For instance, a review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not". Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one isoform. **No genes showed a significant negative correlation**. It is not surprising that not all isoforms are positively correlated with mRNA expression. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

The same authors in Chen *et al.*, published a later paper, Beer *et al.*, (previously provided) which described gene expression of genes in adenocarcinomas and compared that to protein expression. In this paper they report that " these results suggest that the oligonucleotide microarrays provided reliable measures of gene expression" (page 817). The authors also state, "these studies indicate that many of the genes identified using gene expression profiles are likely relevant to lung adenocarcinoma".

The Examiner cites Hanna and Mornin as showing that gene amplification does not reliably correlate with polypeptide over-expression and thus the level of polypeptide expression must be tested empirically. Applicants disagree. Hanna and Mornin describe HER-2/neu Breast cancer predictive testing methods which have been FDA approved: immunohistochemistry and fluorescent in situ hybridization. While Hanna and Mornin indicate that some subsets of tumors were found lacking protein overexpression with gene amplification, Hanna and Mornin state that "in general, FISH and IHC results correlate well." (Column 2) Accordingly, it is more likely than not that protein expression with correlate with gene amplification.

The Examiner has cited Haynes *et al.*, Gygi *et al.*, Lian *et al.*, Fessler *et al.*, and Greenbaum *et al.*, as allegedly showing that increased mRNA levels do not correlate with increased protein levels in healthy tissues.

The Examiner has cited Haynes *et al.* as providing evidence that there is "**no strong correlation** between polypeptide and transcript level. Applicants submit that it is not a legal requirement to establish a necessary or "strong" correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state, nor is it imperative to find evidence that DNA amplifications are always associated with overexpression of the gene product. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is whether it is more likely than not that a person of ordinary skill in the art would recognize a positive correlation. Contrary to the Examiner's reading, Haynes *et al.* teaches that "there was a ***general trend*** but no strong correlation between protein [expression] and transcript levels" (Emphasis added).

The Examiner refers to the references of Gygi et al., Lian et al., Fessler et al., and Greenbaum et al. as allegedly showing a lack of correlation between mRNA expression and protein expression. Applicants disagree that these references show that mRNA levels do not predict protein levels for the reasons set forth herein.

The Examiner Gygi *et al.* as allegedly concluding "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value, the protein levels varied by more than 20-fold.... Our results clearly delineate the technical boundaries of current

approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient."

Applicants further submit that Gygi *et al* too did not indicate that a correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient in **accurately** predicting protein level from the level of the corresponding mRNA transcript (Emphasis added) (see page 1270, Abstract). *Accurate prediction* is not a criteria that is necessary for meeting the utility standards. In fact, contrary to the Examiner's statement, the Gygi data also indicates **a general trend** of correlation between protein [expression] and transcript levels (Emphasis added). For example, as shown in Figure 5, the mRNA abundance of **250-300** copies /cell correlates with the protein abundance of **500-1000** x 10^3 copies/cell. The mRNA abundance of **100-200** copies/cell correlates with the protein abundance of **250-500** x 10^3 copies/cell (emphasis added). Therefore, high levels of mRNA **generally** correlate with higher levels of proteins. In fact, most data points in Figure 5 did not deviate or scatter away from the general trend of correlation. Furthermore, Gygi *et al.* studied yeast cells and not the difference in expression between normal human and lung tumor cells. *Thus*, the Gygi data, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Gygi *et al.*

Applicants again enclose the Futcher reference (Exhibit 13) in response to the citation of Gygi. Futcher *et al.* (Mol. Cell. Biol. 19:7357-7368 (1999)) analyzed the yeast proteome using 2D gel electrophoresis, gathering quantitative data on protein abundance for about 1,400 spots. This data was compared to mRNA abundance for each gene as determined both by SAGE (serial analysis of gene expression) and by hybridization of cRNA to oligonucleotide arrays. The authors concluded that "**several statistical methods show a strong and significant correlation between mRNA abundance and protein abundance**" (page 7360, col. 2; emphasis added).

The authors note that Gygi *et al.* completed a similar study that generated broadly similar data, but reached different conclusions. Futcher *et al.* note that this is in part a difference in viewpoint, in that "Gygi *et al.* focus on the fact that the correlations of mRNA and codon bias with protein abundance are far from perfect" (page 7367, col. 1). Applicants respectfully submit that a showing that mRNA levels can be used to "accurately predict" the precise levels of protein

expression is not required. Applicants need only show that there is a correlation between mRNA and protein levels, such that mRNA overexpression generally predicts protein overexpression. The data of both Futcher *et al.* and Gygi *et al.* clearly meets this standard.

The Examiner Lian *et al.* as allegedly showing a similar lack of correlation in mammalian (mouse) cells. "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels".

Regarding Lian *et al.*, Applicants submit that they only teach that protein expression may not correlate with mRNA level in differentiating myeloid cells and does not teach anything regarding such a lack of correlation for genes in general. In addition, the authors themselves admit that there are a number of problems with the data presented in this reference. At page 520 of this article, the authors explicitly express their concerns by stating that "[t]hese data must be considered with several caveats: membrane and other hydrophobic proteins and very basic proteins are not well displayed by the standard 2DE approach, and **proteins presented at low level will be missed**. In addition, to simplify MS analysis, we used a Coomassie dye stain rather than silver to visualize proteins, and this **decreased the sensitivity of detection of minor proteins.**" (Emphasis added). It is known in the art that Coomassie dye stain is a very insensitive method of measuring protein. This suggests that the authors relied on a very insensitive measurement of the proteins studied. The conclusions based on such measurements can hardly be accurate or generally applicable.

The Examiner also asserts that Fessler *et al.*, who examined lipopolysaccharide-activated neutrophilins, "found a 'poor concordance between mRNA transcript and protein expression changes' in human cells." .

Again, as with Lian *et al.*, Fessler *et al.* only examined the expression level of **a few proteins/RNAs** in response to LPS stimulation. Additionally, the PTO has overlooked a number of limitations of the study by Fessler *et al.* For example, as admitted by Fessler *et al.*, protein identification by two-dimensional PAGE is limited to well-resolved regions of the gel, may perform less well with hydrophobic and high molecular weight proteins, and tends to select for more abundant protein species (page 31301, col. 1). Harvesting of the LPS-incubated PMNs at 4 hours may have prevented detection of earlier, **transient changes and may have thereby**

introduced artificial transcript-protein discordance. Furthermore, the post-LPS incubation, pre-two-dimensional PAGE cell washes **would be expected to remove secreted proteins from further analysis**. In addition, because protein binding of Coomassie Blue has a limited dynamic range and is typically not linear throughout the range of detection, image analysis of Coomassie Blue-stained protein spots should only be consider as semi-quantitative (see page 31301, col. 1). Again, in this study, low abundance proteins were underrepresented. Therefore, Fessler's study cannot be applied to the present application.

In summary, both Fessler *et al.* and Lian *et al.* have relied on insensitive and inaccurate methods of measuring protein expression levels. The teachings of these two references cannot be relied upon to establish a *prima facie* showing of lack of utility.

The Examiner has cited Greenbaum *et al.* as establishing that mRNA levels cannot predict protein levels. In response, Applicants note that Greenbaum is also comparing the expression of a number of different mRNAs and their corresponding proteins in yeast cells and not comparing the change of expression of specific mRNAs and their corresponding proteins in cancer cells versus normal cells. Accordingly, this reference is also not relevant to the issue at hand. Nevertheless, Greenbaum states that logically "we would assume that those ORFs that show a large degree of variation in their expression are controlled at the transcriptional level. The variability of the mRNA expression is indicative of the cell controlling the mRNA expression at different points of the cell cycle to achieve the resulting and desired protein. **Thus we would expect and we found a high degree of correlation (r-0.89) between the reference mRNA and protein levels for these particular ORFs: the cell has already put significant energy into dictating the final level of protein through tightly controlling the mRNA expression**. (page 117.5 1st column). Furthermore, Greenbaum states : **"we found that ORFs that have higher than average levels of ribosomal occupancy – that is that a large percentage of their cellular mRNA concentration is associated with ribosomes (being translated) – have well correlated mRNA and protein expression levels. (Figure 2)."** Therefore, contrary to the Examiner's assertion, Greenbaum does find high levels of correlation between mRNA and protein expression in yeast cells.

For the reasons given above, Applicants respectfully submit that the Examiner has not established a *prima facie* showing of lack of utility based on the references cited in the Office Action and therefore, the Patent Office has failed to meet its initial burden of proof.

Applicants submit herewith further evidence that increased mRNA expression in cancer as compared to normal tissues is correlated with increased protein expression in the same cancerous tissues as compared to normal tissues.

The Examiner indicates that the first Polakis Declaration (Polakis I) is not found persuasive in regard to utility. The Examiner states that there is strong opposing evidence showing that increased mRNA levels are frequently not predictive of increased polypeptide levels.

Applicants again respectfully submit that the standard of proof is not "necessarily correlative" but more likely than not. As Dr. Polakis states, Genentech scientists have found that in approximately **80%** of their observations, an increase in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA. Therefore, while the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard.

Applicants had previously presented a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As stated in paragraph 5 of Dr. Polakis' Declaration (Polakis II):

> "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA."

In support of the assertion that changes in mRNA are correlated to changes in protein levels, Paul Polakis, Ph.D., states in paragraph 6 of his 2nd Declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4-5 above and my knowledge of the

relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor tissue relative to a normal tissue more often than not correlates to a similar increase in abundance of the encoded protein in the tumor tissue relative to the normal tissue. In fact, *it remains a generally accepted working assumption in molecular biology that increased mRNA levels are more often than not predictive of elevated levels of the encoded protein.* (Emphasis added).

Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

The Examiner states that the second Polakis Declaration is insufficient to overcome the rejection because the PRO269 does not appear in the table of Exhibit B of the Declaration. It allegedly is unclear how the clones appearing in the table compare to PRO269. Applicants respectfully disagree. The Declaration and evidence is being offered in support of the statement that it remains a generally accepted working assumption that increased mRNA levels are more often than not predictive of elevated levels of the encoded protein. The Declaration has probative value regardless of whether PRO269 is included in the table.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[5] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"[6] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"[7]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[8] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered."

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[5] *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[6] *In re Alton,* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[7] *In re Alton, supra.*

[8] Part IIB, 66 Fed. Reg. 1098 (2001).

Applicants further enclose a Declaration by Dr. Randy Scott ("the Scott Declaration). Dr. Scott was a co-founder of Incyte Pharmaceuticals, Inc., the world's first genomic information business, and is currently the Chairman and Chief Executive Officer of Genomic Health, Inc., a life sciences company located in Redwood City, California, which provides individualized information on the likelihood of disease recurrence and response to certain types of therapy using gene expression profiling. Based on his more than 15 years of personal experience with the DNA microarray technique and its various uses in the diagnostic and therapeutic fields, and his familiarity with the relevant art, Dr. Scott unequivocally confirms that, as a general rule, there is a good correlation between mRNA and protein levels in a particular tissue.

As stated in paragraph 8 of the Scott Declaration:

> DNA microarray analysis has been extensively used in drug development and in diagnosis of various diseases. ..... Due to its importance in drug discovery and in the field of diagnostics, microarray technology has not only become a laboratory mainstay but also created a world-wide market of over $600 million in the year of 2005. A long line of companies, including Incyte, Affymetix, Agilent, Applied Biosystems, and Amersham Biosciences, made microarray technology a core of their business.

In paragraph 10 of his Declaration, Dr. Scott explains the reasons for the wide-spread use and impressive commercial success of this technique, stating:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, **it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue**. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels. (emphasis added).

The Declaration, which is based on Dr. Scott's unparalleled experience with both the microarray technique and its industrial and clinical applications, supports Applicant's position that the microarray technology is not only mature, reliable and well-accepted in the art, but also has been extensively used in drug development and in diagnosis of various diseases and produced enormous commercial success. Therefore, if a gene, such as the gene encoding the

PRO269, has been identified to be amplified in a certain disease, such as lung cancer, it is more likely than not that the protein product is also overexpressed in the disease.

The statements of Dr. Polakis and Dr. Scott are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (herein after Cell 3rd) and (4th ed. 2002) (herein after Cell 4th) (excerpts attached as Exhibit 1). Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (Emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (Emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (Emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (copy enclosed under Exhibit 1) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848

(Emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004 (copy enclosed in Exhibit 1). Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" *Zhigang* at 2. Of the samples tested, 79 out of 88 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human Pca, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." *Zhigang* at 8. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 9

Further, Meric *et al.*, Molecular Cancer Therapeutics, 1:971-979 (2002), (a copy enclosed in Exhibit 1), states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (Emphasis added).

Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (attached hereto as Exhibit 2), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in

protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 3) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 4) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 5) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the

seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 6) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 7) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci.

Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 8). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Mizrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 9) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 10), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants'

assertion that changes in mRNA level, *e.g.,* a decrease, lead to a corresponding change in the level of the encoded protein, *e.g.,* a decrease.

In an article by Gou and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 11) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, *e.g.,* an increase, generally leads to a corresponding change in the level of protein expression, *e.g.,* an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an additional 70 references (abstracts attached as Exhibit 12) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility. As discussed previously, Applicants have challenged the relevance of references such as Haynes *et al.*, which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to rely on such references, Applicants are submitting references which report results that are contrary to the PTO's cited references and offer indirect support for Applicants' asserted utility.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 14) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 15) the authors examined the expression of three somatostatin receptors

(SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 16) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 17) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 18) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression of BCL2 transcripts commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 19) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 20) which also support Applicants' assertion in that they report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 113 references in addition to the

declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein.

As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 21). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

Together, the declarations of Polakis and Scott and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO269 gene, that the PRO269 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the PRO269 polypeptides and antibodies have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the polypeptide for diagnosis of cancer.

Accordingly, this rejection under 35 U.S.C. §101 and §112, first paragraph, should be withdrawn.

CONCLUSION

For the reasons given above, Applicants submit that the gene amplification assay disclosed in Example 92 of the specification, and the advanced state of the art in oncology,

provide at least one patentable utility for the PRO269 polypeptides of Claims 44-46 and 49-52, and that one of ordinary skill in the art would understand how to use the claimed polypeptides and would have found such testing routine and not 'undue.' Therefore, Claims 44-46 and 49-52 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-1618 P2C33**).

Respectfully submitted,

Date: August 21, 2006

By: _____
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DECLARATION OF RANDY SCOTT, Ph.D. UNDER 37 C.F.R. § 1.132

I, Randy Scott, Ph.D. declare and say as follows:

1. I hold a Bachelor or Science degree in Chemistry from Emporia State University ~~and a Ph.D. in Biochemistry from the University of Kansas.~~

2. I am Chairman and Chief Executive Officer of Genomic Health, Inc., a life science company founded in August of 2000 located in Redwood City, California, conducting sophisticated genomic research to develop clinically validated molecular diagnostics, which provide individualized information on the likelihood of disease recurrence and response to certain types of therapy.

3. In 1991, I co-founded Incyte Pharmaceuticals, Inc., the world's first genomic information business. I served the company in multiple capacities, including Chairman of the Board from August 2000 to December 2001, President from January 1997 to August 2000, and Chief Scientific Officer from March 1995 to August 2000. Under my leadership, Incyte has created the LifeSeq Gold® gene sequence and expression database, an industry standard and the most comprehensive collection of biological information in the world. I have also led Incyte to expand its focus beyond gene sequence databases to include the research and application of gene expression, SNPs (single nucleotide polymorphisms), and proteomics.

4. I am an inventor on several issued patents, and authored over 40 scientific publications in the fields of protein biology, gene discovery, and cancer.

5. My Curriculum Vitae is attached to and serves part of this Declaration.

6. All statements made in this Declaration are based on my more than 15 years of personal experience with the DNA microarray technique and its various uses in the diagnostic and therapeutic fields, and my familiarity with the relevant art.

7. The DNA microarray technology is based on hybridizing arrayed nucleic acid probes of known identity with target nucleic acid to determine the identity and/or expression levels (abundance) of target genes. DNA microarrays work by exploiting the ability of a given

mRNA molecule to hybridize to the DNA template from which it originated. By using an array containing many DNA samples, scientists can determine, in a single experiment, the expression levels of hundreds or thousands of genes within a sample by measuring the amount of mRNA bound to each site on the array. The amount of mRNA bound to the spots on the microarray is ~~precisely measured, generating a profile of gene expression in the sample.~~

8. DNA microarray analysis has been extensively used in drug development and in diagnosis of various diseases. For instance, if a certain gene is over-expressed in a particular form of cancer relative to normal tissue, researchers use microarray chips to determine whether a drug candidate will reduce over-expression, and thereby cause cancer remission. In addition, if a gene has been identified to be over-expressed in a certain disease, such as a certain type of cancer, it can be used to diagnose that disease. Due to its importance in drug discovery and in the field of diagnostics, microarray technology has not only become a laboratory mainstay but also created a world-wide market of over $600 million in the year of 2005. A long line of companies, including Incyte, Affymetix, Agilent, Applied Biosystems, and Amersham Biosciences, made microarray technology a core of their business.

9. Correlation between mRNA and protein levels can be assessed by a variety of methods suitable for measuring protein expression levels, including, for example, SDS-polyacrylamide gel electrophoresis (SDS-PAGE), two-dimensional fluorescence-difference gel electrophoresis (DIGE), mass spectrometric approaches, microsequencing, and a combination of these and similar known techniques, however, direct measurement of protein expression levels remains non-trivial.

10. One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Patent.

Date: August 11, 2006

Randy Scott, Ph.D.

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8/11/06 11:00 AM (39766.7000)

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EDUCATION:

1979 B.S., Chemistry, Emporia State University, Emporia Kansas
1983 Ph.D., Biochemistry, University of Kansas, Lawrence Kansas

WORK EXPERIENCE:

2000-present **GENOMIC HEALTH, INC., Cofounder**

- *Chairman & CEO, (2000-present)*
  Founded a new genomics company and raised over $100 million to bring personalized medicine to clinical practice. Selected by Red Herring Magazine as one of the Top 100 private technology companies in North America in 2005

1991-2000 **INCYTE, Cofounder**

- *Chairman of the Board (2000-2001)*
  Helped lead the transition to a new management team and transition to drug development
- *President and Chief Scientific Officer (1997-2000)*
  Responsible for Research & Development, Operations, Marketing & Sales. Built the world's first genomic information business with peak sales of over $200 million per year including 19 out of the worlds top 20 pharmaceutical companies as subscribers
- *Vice President and Chief Scientific Officer (1991-1997)*
  Built recombinant DNA therapeutic product portfolio and led the launch of the genomics business

1985-91 **INVITRON CORPORATION**

- *Sr. Director of Research (1998-1991)*
  Responsible for Research & Development.
- *Director of Protein Biochemistry (1985-1988)*
  Responsible for building the protein purification group for a cGMP manufacturing facility producing recombinant proteins, including monoclonal antibodies, tPA and Factor VIII.

1983-85 **UNIGENE LABORATORIES, Fairfield, New Jersey**

- *Sr. Scientist, Dept. of Protein Biochemistry*
  Led effort to work on IgA proteases linked to meningococcal infections

OTHER EXPERIENCE:

2005- Present **AMERICAN CLINICAL LABORATORY ASSOCIATION**

- *Member, Board of Directors*

1997-2000 **DIADEXUS, INC., Cofounder**

- *Member, Board of Directors, (1997-2000)*
  Worked with George Poste (CSO, SmithKline, Beecham) to establish a diagnostics joint venture between Incyte and SmithKline

Awards:

2001 Genome Technology Magazine 2001 All-Star
1999 Forbes Magazine list of Biotech's Top 25 Influential Insiders

1997 Ernst & Young/NASDAQ Silicon Valley Entrepreneur of the Year for Life Sciences
1987 Small Business Innovation Research Grant Award (Principal Investigator): "Azurophil-Derived Bactericidal Factor" Grant # SSS-5 (K) 1R43AI24409-011987
1983 Phillip Newmark Research Award, University of Kansas, 1983
1982 Borgendale Graduate Seminar Award, University of Kansas.

Publications:

Low, D.A., Cunningham, D.D., **Scott, R.W.**, and Baker, J.B., "Interactions of Serine Proteases with Human Fibroblasts: Regulation by Protease Nexin, A Cellular Component with Similarities to Antithrombin III." in Receptor-Mediated Binding and Internalization of Toxins and Hormones (Middlebrook, J.L. and Kohn, L.S. eds.) pp. 259-270, Academic Press, New York (1982).

Low, D.A., **Scott, R.W.**, Baker J.B., and Cunningham, D.D., Cells Regulate their Mitogenic Response to Thrombin through Release of Protease Nexin. Nature 298, 476-478 (1982).

Scott, R.W. ,"Purification, Characterization, and Functional Studies of Protease Nexin." Ph.D. Thesis, University of Kansas (1983).

Scott, R.W., Eaton, D.L., Duran, N. and Baker, J.B. Regulation of Extracellular Plasminogen Activator by Human Fibroblasts. The Role of Protease Nexin. J. Biol. Chem. 258, 4397-4403 (1983).

Scott, R.W., and Baker, J.B., Purification of Human Protease Nexin. J.Biol. Chem. 258, 10439-10444 (1983).

Eaton, D.L., **Scott, R.W.**, and Baker, J.B., Purification of Human Fibroblast Urokinase Proenzyme and Analysis of its Regulation by Proteases and Protease Nexin. J. Biol. Chem. 259, 6241-6247 (1984).

Scott, R.W., Bergman, B., Bajpai, A., Hersh, R., Rodriquez, H., Jones, B.N., Barreda, C., Watts, S., and Baker, J.B. Protease Nexin: Properties and a Modified Purification Procedure. J.Biol. Chem. 7029-7034 (1985).

Bergman, B.L., **Scott, R.W.**, Bajpai, A., Watts, S., and Baker, J.B., Inhibition of Tumor-Cell Extracellular Matrix Destruction by a Fibroblast Proteinase Inhibitor, Protease Nexin I. Proc. Nat. Acad. Sci. 83, 996-1000 (1986).

Cance, W.G., Wells, S.A., Dilley, W.G., Welch, M.J., Otsuka, F.L., **Scott, R.W.**, and Davie, J.M., Unique Parathyroid Membrane Antigen(s): Radiolocalization with Specific Monoclomal Antibodies. Surgical Form 37, 410-412 (1986).

Scott, R.W., Duffy, S.A., Moellering, B.J., and Prior, C., Purification of Monoclonal Antibodies from Large-Scale Mammalian Cell Culture Perfusion Systems. Biotechnology Progress 3, 49-56 (1987).

Baker, J.B., McGrogan, M., Simonsen, C.C., **Scott, R.W.**, Gronke, R.S. and Honeyman, A., "Protease Nexin I. Structure and Potential Functions." In The Pharmacology and Toxicology of Proteins, Winkelhake, J.L., Holcenberg, J.S., eds., Alan R. Liss, Inc., New York, (1987).

Scott R.W., "Large-scale Production of Biopharmaceuticals from Mammalian Cells" in Clinical Applications of Genetic Engineering (Larry C. Lasky and JoAnn Edwards-Moulds eds.) American Association of Blood Banks, Arlington, Virginia (1987).

McGrogan, M., Kennedy, J., Li, M.P., Hsu, C., **Scott, R.W.**, Simonsen, C.C., and Baker, J.B., Molecular Cloning and Expression of Two Forms of Human Protease Nexin I, Bio/Technology 6: 172 (1988).

Otsuka FL, Cance WG, Dilley WG, **Scott RW**, Davie JM, Welch MJ, Wells SA Jr., A Potential New Radiopharmaceutical for Parathyroid Imaging: Radiolabeled Parathyroid-specific Monoclonal Antibody –I.

Evaluation of 125-I-labeled Antibody in a Nude Mouse Model System. Int. J. Rad. Appl. Instrum. B. 15:305-11, 1988

Otsuka FL, Cance WG, Dilley WG, **Scott RW**, Davie JM, Wells SA Jr., Welch MJ A Potential New Radiopharmaceutical for Parathyroid Imaging: Radiolabeled Parathyroid-specific Monoclonal Antibody – II. Comparison of 125-I and 111-In-labeled Antibodies. Int. J. Rad. Appl. Instrum. B. 15:305-11, 1988

Prior, C.P., Doyle, K.R., Duffy, S.A., Hope, J.A., Moellering, B.J., Prior, G.M., **Scott, R.W.** and Tolbert, W.R. The Recovery of Highly Purified Biopharmaceuticals from Perfusion Cell Culture Bioreactors. J. Parenteral Science and Technology 43: 15-23 (1989).

McGrogan, M., Simonsen, C., **Scott, R.**, Griffith, J., Ellis, N., Kennedy, J., Campanelli, D., Nathan, C., and Gabay, J., Isolation of a Complementary DNA Clone Encoding a Precursor to Human Eosinophil Major Basic Protein. J. Exp. Med. 168: 2295-2308 (1988).

Wilde, C.G., Griffith, J.E., Marra, M.N., Snable, J.L. and **Scott R.W.**, Purification and Characterization of Human Neutrophil Peptide 4, a Novel Member of the Defensin Family, J. Biol. Chem. 264: 11200-11203 (1989).

Gabay, J.E., **Scott, R.W.**, Campanelli, D., Griffith, J., Wilde, C., Marra, M.N., Seeger, M., and Nathan, C.F., Antibiotic Proteins of Human Polymorphonuclear Leukocytes, Proc. Natl. Acad. Sci. 86: 5610-5614 (1989).

Marra , M.N., Wilde, C.G., Griffith, J.E., Snable, J.L., and **Scott R.W.**, Bactericidal/Permeability-Increasing Protein has Endotoxin Neutralizing Activity, J. Immunol. 144, 662-666 (1990)

Wilde, C.G., Snable, J.L., Griffith, J.E., and **Scott R.W.** Characterization of Two Azurophil Granule Proteases with Active Site Homology to Neutrophil Elastase, J. Biol. Chem. 265: 2038-2041 (1990).

Moellering, B.J., Tedesco, J.L., **Scott, R.W.**, Towensend, R.R., Hardy, M.R., and Prior C.P. Molecular Differences Observed in a Monoclonal Antibody Expressed in Ascites Fluid, Serum-containing and Serum-free Cell Culture Conditions. Biopharm. pp. 30-38 February (1990).

McGrogan, M., Kennedy, J., Golini, F., Ashton, N., Dunn, F., Bell, K., Tate, E., **Scott, R.W.**, and Simonsen, C.C., "Structure of the Human Protease Nexin Gene and Expression of Recombinant forms of PN-1." in Serine Proteases and Serpins in the Nervous System (B.W. Festoff ed.) pp.147-161 Plenum Press New York (1990).

Pereira, H.A., Spitznagel, J.K., Winton, E.F., Shafer, W.M., Martin, L.E., Guzman, G.S. Pohl, J., **Scott, R.W.**, and Kinkade, J.M. Jr. The Ontogeny of a 57KD Cationic Antimicrobial Protein of Human Polymorphonuclear Leukocytes: Localization to a Novel Granule Population. Blood 76:825-834, 1990.

Evans DL, McGrogan M, **Scott RW**, Carrell RW, Protease Specificity and Heparin Binding and Activation of Recombinant Protease Nexin I, J. Biol. Chem. 266:22307-12, 1991

Marra, M,N, C.G. Wilde, M.S. Collins, J.L. Snable, M.B. Thornton, and **R.W. Scott,** The Role of Bactericidal/Permeability-Increasing Protein as a Natural Inhibitor of Bacterial Endotoxin. J. of Immunol. 148:532-537, 1992.

Scott R. W., Wilde C.G., Lane J.C., Snable, J.L., and Marra M.N., "Antimicrobial and Antiendotoxin Activities of Bactericidal/Permeability-Increasing Protein In Vitro and In Vivo" in Bacterial Endotoxin: Recognition and Effector Mechanisms (J. Levin, C.R. Alving, R.S. Munford, and P.L. Stutz eds.) pp. 373-377 Elsevier Science Publishers B.V. (1993)

Stevens, P., **Scott R.W.**, Shatzen E.M., Recombinant Human Protease Nexin-1 Prevents Articular Cartilage Degradation in the Rabbit Agents and Actions Suppl 39:173-7 in press 1993

Marra M.N., Thornton, M.B., Snable, J.L., Leong S., Lane J., Wilde C.G., and **Scott R. W.**, Regulation of the Response to Bacterial Lipopolysaccharide by Endogenous and Exogenous Lipopolysaccharide Binding Proteins" Blood Purif. 11:134-140, 1993

Scott RW, Sequencing the Human Genome (letter), Science 30 260:606-7 1993

Marra M.N., Thornton M.B., Snable J.L., Wilde C.G., **Scott R.W.**, Endotoxin-binding and -neutralizing Properties of Recombinant Bactericidal/Permeability-Increasing Protein and Monoclonal Antibodies HA-1A and E5 Critical Care Medicine 22:559-65, 1994

Fisher CJ Jr., Marra MN, Palardy JE, Marchbanks CR, **Scott RW**, Opal SM Human Neutrophil Bactericidal/Permeability-Increasing Protein Reduces Mortality Rate from Endotoxin Challenge: a Placebo-Controlled Study. Crit Care Med 22:553-8, 1994

Rogy MA, Oldenburg HS, Calvano SE, Montegut WJ, Stackpole SA, Van Zee KJ, Marra MN, **Scott RW**, Seilhammer JJ, Moldawer LL. The Role of Bactericidal/Permeability-Increasing Protein in the Treatment of Primate Bacteremia and Septic Shock. J Clin. Immunol. 14: 120-33, 1994

Calvano SE, Thompson WA, Marra MN, Coyle SM, de Riesthal HF, Trousdale RK, Barie PS, **Scott RW**, Moldawer LL, Lowry SF, Changes in Polymorphonuclear Leukocyte Surface and Plasma Bactericidal/Permeability-Increasing Protein and Plasma Lipopolysaccharide Binding Protein During Endotoxemia or Sepsis. Arch Surg. 129:220-6, 1994

Wilde, G.G., Seilhamer, J.J., McGrogan, M., Ashton, N., Snable, J.L., Lane JC, Leong, SR, Thornton, MB, Miller, KL, **Scott RW**, and Marra, MN "Bactericidal/Permeability-Increasing Protein and Lipopolysaccharide (LPS)-Binding Protein: LPS Binding Properties and Effects on LPS-Mediated Cell Activation" J. Biol. Chem. 269:17411-17416, 1994

Wilde CG, Hawkins PR, Coleman RT, Levine WB, Delegeane AM, Okamoto PM, Ito LY, **Scott RW**, Seilhamer JJ, DNA Cell Biol. 13:711-8, 1994

Opal SM, Palardy JE, Marra MN, Fisher CJ Jr., McKelligon BM, **Scott RW** Lancet 344:429-31 1994

Yang, JH, Marsters, S., Ashkenazi A., Bunting S, Marra MN, **Scott RW**, Baker JB Protection against endotoxic shock by Bactericidal/permeability-increasing Protein in Rats, J. Clin. Invest. 95:1947-52, 1995

Zweiger, G., **Scott R.W.**, From Expressed Sequence tags to "epigenomics": an Understanding of Disease Processes. Curr. Opin. Biotechnology 8:684-7, 1997

Scott RW, Gene Patents and Other Genomic Inventions. Published Hearing before the Subcommittee on Courts and Intellectual Property of the Committee on the Judiciary House of Representatives, One Hundred Sixth Congress, Second Session, July 13, 2000 Serial No. 121. pp. 44-55 . U.S. Government Printing Office Washington, 2000

Issued Patents:

U.S. Patent # 4,898,826 Issued Feb. 6, 1990
A Method for Solubilization of Tissue-Type Plasminogen Activator.

U.S. Patent # 5,006,252 Issued April 9, 1991
Recombinant Purified Protease Nexin.

U.S. Patent #5,032,574 Issued July 16, 1991
Novel Antimicrobial Peptide, Compositions Containing Same and Uses Thereof.

U.S. Patent #5,087,368 Issued Feb. 11, 1992
Purified Protease Nexin

U.S. Patent #5,089,274 Issued Feb. 18, 1992
Use of Bactericidal/Permeability Increasing Protein or Biologically Active Analogs Thereof to Treat Endotoxin-Related Disorders

U.S. Patent #5,112,608 Issued May 12, 1992
Use of Protease Nexin-1 to Mediate Wound Healing

U.S. Patent #5,171,739 Issued December 15, 1992
Treatment of Endotoxin-Associated Shock and Prevention Thereof Using a BPI Protein

U.S. Patent #5,187,089 Issued Feb. 16, 1993
Protease Nexin-1 Variants Which Inhibit Elastase

U.S. Patent #5,196,196 Issued March 23, 1993
Use of Protease Nexin-1 in Wound Dressings

U.S. Patent #5,206,017 Issued Apr. 27, 1993
Use of Protease Nexin-1 as an Anti-inflammatory

U.S. Patent #5,210,027 Issued May 11, 1993
DNA Encoding Novel Antimicrobial Polypeptide and Methods for Obtaining Such Polypeptide

U.S. Patent #5,278,049 Issued January 11, 1994
Recombinant Molecule encoding Human Protease Nexin

U.S. Patent #5,234,912 Issued August 10, 1993
Pharmaceutical Compositions Comprising Recombinant BPI Proteins and a Lipid Carrier and Uses Thereof

U.S. Patent #5,278,049 Issued January 11, 1994
Recombinant Molecule encoding Human Protease Nexin

U.S. Patent #5,308,834 Issued May 3, 1994
Treatment of Endotoxin-Associated Shock and Prevention Thereof Using BPI Protein

U.S. Patent #5,326,562 Issued July 5, 1994
Pharmaceutical Dosage Unit for Treating Inflammation Comprising Protease Nexin-I

U.S. Patent #5,234,912 Issued August 10, 1993
Pharmaceutical Compositions Comprising Recombinant BPI Proteins and a Lipid Carrier and Uses

U.S. Patent #5,278,049 Issued January 11, 1994
Recombinant Molecule Encoding Human Protease Nexin

U.S. Patent #5,326,562 Issued July 5, 1994
Pharmaceutical Dosage Unit for Treating Inflammation Comprising Protease Nexin-1

U.S. Patent #5,334,584 Issued August 2, 1994
Recombinant, Non-Glycosylated BPI Protein and Uses Thereof

U.S. Patent #5,457,090 Issued October 10, 1995
Protease Nexin-I Variants

U.S. Patent #5,470,825 Issued November 28, 1995
Basophil Granule Proteins

U.S. Patent #5,476,839 Issued December 19, 1995

Basophil Granule Proteins

U.S. Patent #5,495,001 Issued February 27, 1996
Recombinant Purified Protease Nexin

U.S. Patent #5,747,283 Issued May 5, 1998
Basophil Granule Proteins

U.S. Patent #5,770,694 Issued June 23, 1998
Genetically Engineered BPI Variant Proteins

U.S. Patent #5,840,484 Issued November 24, 1998
Comparative Gene Transcript Analysis

U.S. Patent #6,114,114 Issued September 5, 2000
Comparative Gene Transcript Analysis

U.S. Patent #6,093,801 Issued July 25, 2000
Recombinant Analogs of Bactericidal/Permeability Increasing Protein

U.S. Patent #6,160,104 Issued December 12, 2000
Markers for Peroxisomal Proliferators

U.S. Patent #6,160,105 Issued December 12, 2000
Monitoring Toxicological Responses

U.S. Patent #6,265,187 Issued July 24, 2001
Recombinant Endotoxin Neutralizing Proteins

U.S. Patent #6,403,778 Issued June 11, 2002
Toxicological Response Markers

U.S. Patent #6,372,431 Issued April 16, 2002
Mammalian Toxicological Response Markers

U.S. Patent #6,553,317 Issued April 22, 2003
Relational database and system for storing information relating to biomolecular sequences and reagents